Paper No. 34

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Ex parte NEENA L. SUMMERS,
CHARLES A. MCWHERTER, and YIQING FENG

Appeal No. 2003-0337
Application No. 08/954,954

HEARD: May 6, 2003

Before WINTERS, SCHEINER, and ADAMS, Administrative Patent Judges.

ADAMS, Administrative Patent Judge.

DECISION ON APPEAL

This is a decision on the appeal under 35 U.S.C. § 134 from the examiner's final rejection of claims 1-14, which are all the claims pending in the application.

Claim 1 is illustrative of the subject matter on appeal and is reproduced below:

A human Erythropoietin receptor agonist polypeptide, comprising a modified Erythropoietin amino acid sequence selected from the group consisting of:

(a) the sequence of SEQ ID NO: 121;

(b) a polypeptide sequence comprising residues 7-166 of SEQ ID NO: 121;

(c) a polypeptide sequence comprising residues 1-161 of SEQ ID NO: 121; and

(d) a polypeptide sequence comprising residues 7-161 of SEQ ID NO: 121;

and wherein said modification comprises the linear rearrangement of the sequences of (a)-(d) wherein the N-terminus is joined to the C-terminus directly or through a linker capable of joining the N-terminus to the C-terminus and new C- and N-termini are created between the amino acid reside pairs of SEQ ID NO: 121 selected from the group consisting of:

23-24, 24-25, 25-26, 26-27, 27-28, 28 29, 29-30, 30-31, 31-32, 32-33, 33-34, 34-35, 35 36, 36-37, 37-38, 38-39, 40-41, 41-42, 43-44, 44 45, 45-46, 46-47, 47-48, 48-49, 50-51, 51 52, 52-53, 53-54, 54-55, 55-56, 56-57, 57 58, 77-78, 78-79, 79-80, 80-81, 81-82, 82-83, 84-85, 95-86, 86-87, 87-88, 88-89, 108-109, 109-110, 110 111, 111-112, 112-113, 113-114, 114-115, 115-116, 116 117, 117-118, 118-119, 119-120, 120-121, 121 122, 122 123, 123-124, 124-125, 125-126, 126 127, 127-128, 128-129, 129-130, 130-131, and 131-132; and

wherein said Erythropoietin receptor agonist polypeptide may optionally be immediately preceded by (methionine^{-1}), (alanine^{-1}) or (methionine^{-2}, alanine^{-1})

The references relied upon by the examiner are:

Pastan et al. (Pastan)	5,635,599	Jun. 03, 1997
Lin	4,703,008	Oct. 27, 1987
Cousens et al. (Cousens)	4,751,180	Jun. 14, 1988

Chaudhary et al. (Chaudhary), "A recombinant immunotoxin Consisting of Two Antibody Variable Domains Fused to Pseudomonas Exotoxin," Nature, Vol. 339, pp. 394-396 (1989)

GROUNDS OF REJECTION

Claims 1, 5 and 10-14 stand rejected under 35 U.S.C. § 103 as being unpatentable over Pastan in view of Lin.

Claims 1-4 and 6-9 stand rejected under 35 U.S.C. § 103 as being unpatentable over Pastan in view of Lin, Chaudhary and Cousens.

We affirm.

CLAIM GROUPING

According to appellants (Brief, page 4), the claims, "to the extent separately identified and argued below, do not stand or fall together." Appellants, however, do not separately argue the claims in each ground of rejection. Therefore, we limit our discussion to representative claim 1. Accordingly, the claims in each ground of rejection stand or fall together with claim 1. 37 CFR § 1.192(c)(7) (2001).

DISCUSSION

Pastan in view of Lin:

According to the examiner (Answer, page 4), Pastan "teach ... a modified growth factor amino acid sequence, wherein the modification comprises the linear rearrangement wherein the N-terminus is joined to the C-terminus directly or through a linker capable of joining the N-terminus to the C-terminus and having new C- and N-termini in the middle of the polypeptide...." The examiner finds (id.), Pastan expressly state "that erythropoietin (EPO) is amenable to this procedure, which they term 'circular permutation'...."

The examiner recognizes (id.), however, that Pastan "do not disclose a working example of circularly permuted EPO, nor do they disclose" an EPO sequence. The examiner relies on Lin to make up for this deficiency. According to the examiner (id.), Lin characterized human EPO, and aligned the human and

monkey EPO sequences. In this regard, the examiner finds (id.), Pastan "disclose that a good choice for an 'opening site' (i.e., a new C- and N-termini) is at a site that is tolerant to amino acid substitution or in a region of the protein that does not show highly conserved sequence identity between closely related proteins in an alignment...."

Following the teachings of Pastan, the examiner reviewed Lin and found that differences between the human and monkey sequences "occur at amino acid positions 25, 27, 30, 32, 80, 82, 88, 116, and 121" suggesting "that an opening site would be tolerated in a circularly permuted EPO molecule at any one of these sites." Answer, bridging paragraph, pages 4-5. Based on this evidence, the examiner finds (Answer, page 5), it would have been prima facie obvious to a person of ordinary skill in the art at the time the invention was made to apply the teachings of Pastan to those of Lin to circularly permute a human EPO polypeptide at positions 25, 27, 30, 32, 80, 82, 88, 116, and 121.[1]

In response, appellants argue (Brief, pages 7-8) that Pastan is limited to its working examples of "two circular permutation breakpoints (37-38 and 104-105) of IL-4 (Example 1) and these molecules in the context of a chimeric molecule with a cytotoxin (Example 2 & 4) or an antibody fragment (Fv) (Example 5)." According to appellants (id.), the teachings of the reference should be limited because Pastan did not demonstrate that other circularly

[1] We recognize that appellants' claim 1 identifies more than these nine sites, however, given that the claim is written in Markush format the combination of references only has to suggest the modification of one of these sites. Here all nine amino acid positions identified by the examiner are identical to nine of the positions identified by appellants.

permuted proteins would fold correctly. In this regard, we remind appellants that "a reference is not limited to the disclosure of specific working examples." In re Mills, 470 F.2d 649, 651, 176 USPQ 196, 198 (CCPA 1972).

Appellants argue (Brief, page 8) that Pastan identifies a number of "general options" for the selection of opening sites and therefore merely invites a person of ordinary skill in the art to explore a general approach with no reasonable expectation of success. We disagree. As the examiner explains (Answer, page 8), Pastan "provide the critical parameters regarding choice of opening sites." The examiner relied on column 8, lines 30-54 of Pastan to support her argument. Pastan discloses (column 8, lines 45-50), "[w]here the protein is a member of a family of related proteins, one may infer that the highly conserved sequences are critical for biological activity, while the variable regions are not. Preferred opening sites are then selected in regions of the protein that do not show highly conserved sequence identity between various members of the protein family." Applying Pastan's guidance to the sequence alignment taught by Lin, the examiner identified nine preferred opening sites in human EPO. All nine are identical to opening sites identified by appellants. Accordingly, we are not persuaded by appellants' argument that there is no reasonable expectation of success in obtaining a circularly permuted EPO protein.

Appellants argue (Brief, page 9) "that from this single alignment the [e]xaminer has incorrectly concluded that, at any one of these single residue amino acid substitutions can be made without effecting the bioactivity."

Appellants, however, offer no evidence to support this argument[2], which conflicts with the disclosure in Pastan (column 8, lines 46-48), "one may infer that the highly conserved sequences are critical for biological activity, while the variable regions are not."

Appellants argue (Brief, page 10), "[a] much different picture emerges, as to what may or may not be a non-conserved position, from the comparison of seven species in [Figure 6 of] WO 94/24160." Upon review of Figure 6 of WO 94/24160, we note that the Figure confirms that each of the nine amino acid positions identified by the examiner are nonconserved (variable) amino acid positions. We are not persuaded by appellants' attempt to limit the evidentiary value of the reference by pointing out that when something less than all the sequences are compared certain amino acid positions become conserved regions. The facts in evidence make clear that applying the teaching of Pastan to the sequence comparison of Lin, nine amino acid positions are identified as "opening sites" for circular permutation. These same nine amino acid positions are taught to be variable amino acid positions in WO 94/24160 as well. Accordingly, we are not persuaded by appellants' argument.

Furthermore, to the extent that appellants argue that Pastan suggests that glycosylation sites, non-conserved positions, non-structured regions, substitution-tolerant sites are considered to be good breakpoints, we agree with the examiner (Answer, page 12), Pastan "never state that a potential breakpoint

---

are identical to nine of the positions identified by appellants.

[2] We remind appellants that "[a]rgument of counsel cannot take the place of evidence lacking in the record" Meitzner v. Mindick, 549 F.2d 775, 782, 193 USPQ 17, 22 (CCPA 1977).

site must meet all of the criteria." To the contrary, Pastan expressly disclose (column 8, lines 45-50), "[w]here the protein is a member of a family of related proteins ... [p]referred opening sites are ... selected in regions of the protein that do not show highly conserved sequence identity between various members of the protein family."

Appellants argue (Brief, page 13), Pastan "provides no guidance as to what the criteria are for determining what the crucial regions of EPO are for the folding process, critical elements of the final conformation or the desired activity [sic]." To the contrary, Pastan disclose (column 7, line 66 through column 8, line 19),

> [c]ircular permutation requires that the protein have an opening site ... where the formation of termini will not interrupt secondary structure crucial in the folding process or critical elements of the final conformation ... preferred opening sites will be located in regions that do not show a highly regular three-dimensional structure. Thus, it is preferred that opening sites be selected in regions of the protein that do not show secondary structure such as alpha helices....

While Pastan discloses methods of identifying secondary structure (column 8, lines 20-29), Figure 6 of WO 94/24160, relied upon by appellants, confirms that each of the nine amino acid positions identified by the examiner are not within regions of the "predicted four α-helices in the human sequence." See also description of Figure 6, WO 94/24160, pages 7-8. Accordingly, we are not persuaded by appellants' argument. Instead, we find that the combination of Pastan in view of Lin provides a person of ordinary skill in the art with a

reasonable expectation of success in obtaining a circularly permuted human EPO protein.

For the reasons given by the examiner (Answer, page 15), we are not persuaded by appellants' arguments (Brief, page 14) based on In re Bell, 991 F.2d 781, 26 USPQ2d 1529 (Fed. Cir. 1993), and In re Deuel, 51 F.3d 1552, 34 USPQ2d 1210 (Fed. Cir. 1995). We are also not persuaded by appellants' arguments based on the prosecution history of Pastan. According to appellants (Brief, page 15), "[t]here was no evidence presented [in Pastan] that EPO or any of the other proteins contemplated were enabled and [the] file history clearly established the lack of enablement beyond what was claimed." As discussed, supra, Pastan provides guidance on circularly permuting proteins and expressly states that EPO as well as other growth factors can be circularly permuted. Pastan, column 4, lines 27-44. Accordingly, for the reasons discussed supra, it is our opinion that the combination of Pastan with Lin provides a person of ordinary skill in the art with a reasonable expectation of success in obtaining such a modified human EPO protein.

For the foregoing reasons, it is our opinion that the examiner met her burden of providing the evidence necessary to establish a prima facie case of obviousness. In re Oetiker, 977 F.2d 1443, 1445, 24 USPQ2d 1443, 1444 (Fed. Cir. 1992). Accordingly the burden of coming forward with evidence or argument was properly shifted to the appellants. Appellants, however, failed to carry their burden. Accordingly we affirm the rejection of claim 1 under

35 U.S.C. § 103 as being unpatentable over Pastan in view of Lin. As set forth supra, claims 5 and 10-14 fall together with claim 1.

Pastan in view of Lin, Chaudhary and Cousens:

The examiner relies on Pastan and Lin as discussed above. However, the examiner finds (Answer, page 6), "[n]either reference teaches the specific GlySer-rich linker sequences as required by claims 2-4 and 6-9." The examiner relies on Chaudhary and Cousens to make up for this deficiency.

Initially, we fail to understand why appellants properly identify the evidentiary basis of the rejection (see Brief, page 15, bolded type-face), yet make reference to "Gearing et al. ('180)" (Brief, page 15), and Gearing et al., Lyman and Hannum" (Brief, page 16). None of Gearing et al., Lyman, or Hannum are relied upon in this rejection.

Nevertheless, having found that the examiner properly established a prima facie case of obviousness for claim 1 over the combination of Pastan and Lin, and that claim 1 does not require a linker sequence different than that disclosed by Pastan (see e.g., Pastan, column 7, lines 32-65), we affirm the rejection of claim 1 under 35 U.S.C. § 103 as being unpatentable over Pastan in view of Lin, Chaudhary and Cousens. As set forth supra, 2-4 and 6-9 fall together with claim 1.

No time period for taking any subsequent action in connection with this appeal may be extended under 37 CFR § 1.136(a).

AFFIRMED

Sherman D. Winters)
Administrative Patent Judge)
)
)
Toni R. Scheiner) BOARD OF PATENT
)
Administrative Patent Judge) APPEALS AND
)
) INTERFERENCES
)
Donald E. Adams)
Administrative Patent Judge)

DA/dym

Carol M. Nielsen
Gardere, Wynne, Sewell LLP
Patent Section (H)
1601 Elm Street, Suite 3000
Dallas, TX 75201-4761